REMARKS

I. Claim Status

Applicants hereby add new claims 41-47, amend claims 1, 3, 6, 8, 14-18, 20, 22, 36-38, and 40 to clarify the claimed subject matter, and cancel claims 13, 19 and 39. Applicants reserve the right to pursue the cancelled subject matter in this or a continuing application. Support for the new and amended claims is present in the specification and originally-filed claims at least at, e.g., [065]-[067], [086], [099]-[0101], [0103], [0108], [0130]-[0139], [0181]-[0183], and [0198]. No new matter is added. Thus, upon entry of this amendment, claims 1, 3-4, 6-12, 14-18, 20, 22, 36-38, and 40-47 will be pending, with claims 1, 3-4, 6-9, 14-18, 20, 36-38, and 40-47 under examination. Claims 1, 3-4, 6-9, 14-18, 20, 36-38, and 40 are rejected. Applicants respectfully request entry, consideration and examination of this response and the timely allowance of pending claims 1, 3-4, 6-9, 14-18, 20, 36-38, and 40-47 in view of the arguments set forth below.

II. Rejections Under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 8 and 38 under 35 U.S.C. § 112, second paragraph, as being indefinite because of the use of the term "GL-3." The Examiner noted that "[s]pelling out the term 'GL-3' would be remedial." Office Action at 3. Applicants have amended claims 8 and 38 to clarify that GL-3 is globotriaosylceramide, and thus request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

The Examiner has rejected claims 14 and 40 under 35 U.S.C. § 112, second paragraph, as being indefinite because of the use of the term "AAV." The Examiner noted that "[s]pelling out the term 'AAV' would be remedial." Office Action at 3. Applicants have amended claims 14 and 40 to clarify that AAV is an acronym for "adeno-associated virus," and thus request that the rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

III. Rejections Under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected claims 1, 3-4, 6-9, 13-18, 20, and 36-40 under 35-U.S.C. § 112, first paragraph, for lack of enablement. Office Action at 3. Applicants respectfully traverse.

The test of enablement is whether the disclosure, coupled with information known in the art, allows one skilled in the art to make and use the claimed invention without undue experimentation. *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976). The "[f]actors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Applicants note, however, that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts." *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1213 (Fed. Cir. 1991).

The claimed invention is directed to a method of treating a subject diagnosed as having a lysosomal storage disease (LSD), comprising first administering a gene therapy vector encoding a lysosomal hydrolase under the control of a liver specific promoter, wherein the gene therapy vector is an adeno-associated virus (AAV), and then administering an exogenously produced natural or recombinant lysosomal hydrolase.

In inventing the claimed subject matter, Applicants recognized that "a need exists for defined and improved combination therapies [for lysosomal storage diseases] that overcome significant limitations associated with [gene therapy (GT) and enzyme replacement therapy (ERT)] . . . when used alone." Applicants therefore invented a method of "[a]lternating among GT and ERT . . . [that] provides a strategy for *simultaneously taking advantage of the strengths and addressing the weaknesses*

associated with each therapy employed alone." Specification at [033] (emphasis added).

Applicants have provided adequate guidance in the specification for the skilled artisan to practice the claimed invention, as elaborated *infra*. Further, Applicants provide evidence that the claimed invention is enabled by demonstrating that four distinct lysosomal storage diseases can be treated using the claimed methods.

First, Applicants have provided working Examples 2-9 in the specification, demonstrating that Fabry disease may be successfully treated pursuant to the methods of the invention. Applicants also refer the Examiner to Ziegler et al., *Mol. Ther.* 9:231-240 (2004),[1] further confirming that the claimed methods successfully treat Fabry disease.

Second, Applicants refer the Examiner to Barbon et al., *Mol. Ther.* 12:431-440 (2005) ("*Barbon*"),[2] applying the claimed methods to the treatment of Niemann-Pick disease. *Barbon* demonstrates that the claimed methods successfully treat Niemann-Pick disease.

Third, Applicants refer the Examiner to McEachern et al., *J. Gene Med.* 8:719-729 (2006) ("*McEachern*"). *McEachern* provides data demonstrating that gene therapy using a liver-specific regulatory element (DC172) and an AAV vector, as recited in claim 1, can induce tolerization to glucocerebrosidase and treat a mouse model of Gaucher disease. As noted in the specification, ERT for Gaucher disease has been commercially available since 1991. Specification at [0101]. Accordingly, there can be no doubt that the claimed methods can be successfully employed to treat Gaucher disease.

Finally, Applicants have conducted additional experiments that demonstrate that gene therapy using a liver-specific regulatory element (DC190) and an AAV vector, as

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[1] This document was submitted in an Information Disclosure Statement (IDS) initialed by the Examiner on May 21, 2007.

[2] This document was submitted in an IDS initialed by the Examiner on May 21, 2007.

recited in claim 1, will induce tolerization to α-glucosidase and treat a mouse model of Pompe disease.[3] ERT for Pompe disease had been demonstrated prior to Applicants' filing date (*see* specification at [019]) and, in fact, was later approved for Pompe disease, as demonstrated by the Food and Drug Administration (FDA)-approved treatments Fabrazyme® (Genzyme Corp.) and Replagal™ (Shire). Thus, again, there can be no doubt that the claimed method can be successfully employed to treat Pompe disease.

Therefore, and for the further reasons elaborated below, Applicants submit that the scope of the claims is commensurate with the enablement provided by the disclosure, coupled with the knowledge of the skilled artisan.

A. Lysosomal Storage Diseases

The Examiner alleges that "[t]he state of the art of treating lysosomal storage diseases in vivo was unpredictable at the time of the invention." Office Action at 8. The Examiner bases that allegation on the "diverse lysosomal storage diseases or disorders, the broad scope of heterogeneity of clinical expression within a type of LSD, limited number of enzyme replacement therapy available, and the difficulties in treating LSDs involving CNS." *Id.* at 9. Applicants respectfully disagree for the following reasons. (Applicants will address enzyme replacement therapy in a dedicated section *infra*.)

Applicants note that although lysosomal storage diseases may be "diverse," they share an underlying mechanistic similarity, i.e., the complete or partial lack of enzymatic activity of a particular lysosomal hydrolase. That is, they are "a family . . . that result from different defects in lysosomal function." Fauci et al., eds., *Harrison's Principles of Internal Medicine* (McGraw-Hill, 14th ed., 1998) at 2169. Indeed, "[t]he clinical features of the lysosomal storage diseases can be predicted by knowing the normal site of degradation of the deficient enzyme's substrate and are dependent on the rate and magnitude of accumulation of undegraded material." *Id.* at 2169.

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[3] If the Examiner would prefer that the details of these experiments be submitted in a declaration under Rule 132, Applicants respectfully request the Examiner to contact the undersigned attorney, who will gladly provide this declaration.

Applicants do not dispute that clinical heterogeneity is frequently observed. "In some cases, different mutations in the lysosomal structural genes account for the observed heterogeneity. For example, one mutation . . . may cause total loss of the enzyme activity, whereas another mutation . . . may result in only partial impairment of enzyme activity and a less severe clinical course." *Id.* at 2169-70. In other cases, "[h]eterogeneity . . . is increased by the fact that patients with autosomal recessive traits are frequently compound heterozygotes and inherit two different mutant alleles . . . ." *Id.* at 2170. Nevertheless, such hetereogeneous clinical manifestations do *not* necessitate heterogeneous treatments. Rather, the skilled artisan would readily expect that most, if not all, LSDs can be treated by supplying the missing or deficient enzymatic activity with an appropriate lysosomal hydrolase administered by, e.g., either GT or ERT.

(1) Lysosomal Hydrolases

The Examiner alleges that "[t]he biological function of a protein from mere amino acid sequence was unpredictable at the time of the invention." Office Action at 10. Applicants respectfully note that a skilled artisan would have no difficulty selecting an appropriate sequence, typically the wild-type sequence or a close variant, for use in enzyme replacement therapy or gene therapy. Indeed, the sequences of lysosomal hydrolases were well known as of the priority date. *See, e.g.*, Salvetti et al., *Br. Med. Bull.* 51:106-122 (1995)("*Salvetti*") ("The gene corresponding to the affected enzyme has been identified for most LSD[s] and cDNAs are available . . . ."); Neufeld, *Annu. Rev. Biochem.* 60:257-280 (1991)[4] ("The cloning and characterization of nearly 20 complementary DNAs (cDNAs) and a half dozen genes encoding lysosomal enzymes have been reported to date."); Pastores and Barnett, *Expert Opin. Emerging Drugs* 10:891-902 (2005) ("*Pastores*")[5] ("Most of the genes encoding lysosomal enzymes have been cloned . . . ."). Thus, as in *Monsanto v. Scruggs*, there is a high level of skill in the art and "specific sequences are not required because [lysosomal hydrolases are] well-

[4] This document was submitted in an IDS initialed by the Examiner on May 21, 2007.

[5] This document was cited by the Examiner.

known and well-documented." *Monsanto v. Scruggs*, 459 F.3d 1328, 1338 (Fed. Cir. 2006).

Further, the skilled artisan could easily have selected a sequence other than the wild-type sequence. Methods for generating and testing polypeptide variants were well known in the art as of the filing date of the instant application. *See, e.g.*, Bowie et al., *Science* 247:1306-1310, 1306 (1990); Miller et al., *J. Mol. Biol.* 131:191-222 (1979); Branden et al., *Introduction to Protein Structure*, pp. 358-366 (Garland Publishing, Inc., 2d ed., 1999) (a "small number of active proteins can be separated from millions of inactive variants"). Moreover, the skilled artisan could define conserved regions and identify any significant functional motif(s), without undue experimentation, by comparing the wild-type human sequences to related sequences known at the time of filing, including, e.g., non-human sequences and sequences found in human disease. Conserved amino acids and mutations known to result in disease are more likely to be important for activity; conversely, amino acids that are not conserved indicate regions of the polypeptide that are more likely to tolerate variation. Following these guidelines, the skilled artisan would expect to identify functional variants through no more than routine effort. Accordingly, the selection of an appropriate sequence is routine technology adequately enabled by the literature.

(2) Treatment

The Examiner alleges that "[t]here is no correlation between reduction of GL-3 level in the organs and treatment of Fabry disease in a subject, i.e. amelioration of pathological symptoms of Fabry disease in vivo. Reduction of GL-3 in organs does not necessarily mean that the Fabry disease is treated." Office Action at 10. Applicants respectfully disagree.

Initially, Applicants would like to point out that the FDA and thousands of patients receiving this therapy would strongly disagree with the Examiner's position here. Applicants direct the Examiner's attention to the attached Prescribing Information for Fabrazyme® (Genzyme Corp.), an FDA-approved treatment for Fabry Disease. The Prescribing Information characterizes reduction of "GL-3 inclusions" as "*[t]he primary*

efficacy endpoint" in clinical trials (emphasis added). Thus, as noted above, "experts at the FDA have assessed the rationale for the . . . research study . . . and found it satisfactory." M.P.E.P. § 2107.03. Moreover, Applicants note that the specification *defines* "accumulation of GL-3" as a measure of "disease progression." Specification at [0104].

Applicants further note that Wraith, *J. Inherit. Metab. Dis.* 29:442-447 (2006) ("*Wraith*"), cited by the Examiner, teaches that when "[t]he level of storage within the cells or organs of the individual [is] reduced, "[a]s a consequence . . . the natural history of the disease should be altered favourably." *Wraith* at 443. *Wraith* itself thus teaches that reduction of stored substrates results in treatment of LSDs. Similarly, the skilled artisan would recognize that reduction of stored substrates is a measure of treatment in LSDs generally.

For all of the reasons above, it is clear that the full breadth of the claims with regard to lysosomal storage diseases is adequately enabled, and that the skilled artisan could make and use the claimed invention without undue experimentation. Therefore, Applicants respectfully request that the enablement rejection with regard to lysosomal storage diseases be withdrawn.

B. Gene Therapy

The Examiner alleges that "the state of the prior art [in gene therapy] was not well developed and was highly unpredictable at the time of filing." Office Action at 6.

Applicants do not claim that gene therapy is perfect, as discussed above. Thus, the Examiner's argument that "numerous factors complicate in vivo gene therapy with respect to predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation" is not on point. Office Action at 7. Rather, Applicants' invention is directed to a method that "*overcome[s] significant limitations associated with [gene therapy] . . . when used alone*" (Specification at [025]) and "tak[es] advantage of the strengths and address[es] the weaknesses associated with [gene] therapy employed alone." Specification at [033] (emphasis added).

Nevertheless, as taught by *Salvetti*, the skilled artisan would recognize that "[a]lthough considerable difficulties must be surmounted, LSD[s] present a favourable situation for gene therapy. . . . Low and unregulated levels of enzyme activity should be sufficient for correction. Importantly, a variety of gene transfer strategies can be carefully evaluated in animal models." *Salvetti* at Abstract . Further, the skilled artisan would recognize that "the size of the corresponding cDNAs [of lysosomal enzymes] is generally compatible with their transfer by recombinant vectors." *Pastores* at 897. Finally, the skilled artisan would appreciate that "minimal amounts of intralysosomal enzyme activity appear adequate in preventing substantial tissue substrate accumulation (as evident from the lack of disease among carriers)." *Id.*

Further, the skilled artisan would have been aware of the considerable body of literature regarding gene therapy for lysosomal storage diseases as of the priority date of the subject application. *See, e.g.*, Ziegler et al., *Hum. Gene Ther.* 10:1667-1682 (1999) (gene therapy in murine model of Fabry disease)[6]; Novo et al., *Gene Ther.* 4:488-492 (1997) (gene therapy in murine model of Fabry disease); Stein et al., *J. Virol.* 3424-3429 (1999) (gene therapy in murine model of mucopolysaccharidosis (MPS) VII); Elliger et al., *Gene Ther.* 6:1175-1178 (1999) (gene therapy in murine model of MPS VII). *See also* Torchiana et al., *Neuroreport* 9:3823-3827 (1998) (*in vitro* gene therapy for Krabbe disease); Braun et al., *Proc. Natl. Acad. Sci. USA* 90:11830-11834 (1993) (*in vitro* gene therapy for MPS II); Peters et al., *Biochem. J.* 276:499-504 (1991) (in vitro gene therapy for MPS VI). *See also* specification at [014]-[017].

Finally, the skilled artisan would have been aware of the numerous patents that have been granted by the USPTO (such as, e.g., U.S. Patent Nos. 5,910,488; 5,882,877; 5,836,905; 5,827,703; 5,824,544; 5,756,283) providing methods for performing gene therapy. Thus, Applicants contend that the field of gene therapy, particularly as applied to lysosomal storage disorders, was adequately developed as of the priority date of the present application.

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[6] This document was submitted in an IDS initialed by the Examiner on May 21, 2007.

(1) Tissue-Specific Gene Therapy

The Examiner further alleges that "[w]hile progress has been made in recent years for gene transfer *in vivo*, *vector* targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art." Office Action at 6 (emphasis added). Again, the Examiner's allegation is not on point.

Applicants note that, in the claimed invention, the transgene is not targeted to a particular tissue, although the "*expression* of the transgene [is] regulated by tissue specific regulatory elements." Specification at [025] (emphasis added). Moreover, as amended, the claims recite that the tissue-specific regulatory element is a liver-specific regulatory element. As such, the expression of the transgene controlled by the liver-specific regulatory element is restricted to the liver. To illustrate, Example 6 explains that "despite the delivery of AAV2/DC190-αgal genome to a variety of tissues, expression of α-galactosidase A mRNA was primarily restricted to the liver." Specification at [0203]. Accordingly, the Examiner's argument that "vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient" has no bearing on the issue of enablement.

For all of the reasons above, it is clear that the full breadth of the claims with regard to gene therapy is adequately enabled, and that the skilled artisan could make and use the claimed invention without undue experimentation. Therefore, Applicants respectfully request that the enablement rejection with regard to gene therapy be withdrawn.

C. Enzyme Replacement Therapy

The Examiner suggests that "the state of art of treating lysosomal diseases in vivo was unpredictable at the time of the invention." Office Action at 8. In particular, the Examiner argues that the "limited number of enzyme replacement therapy [sic] available," "the prospect that only partial responses may occur," "the difficulties in treating LSDs involving CNS," and the prospect that "disorders associated with defects in membrane proteins . . . will most likely not [be] responsive to enzyme therapy" are evidence of lack of enablement. Office Action at 8-9. Applicants respectfully disagree.

Enzyme replacement therapy for lysosomal storage diseases was well established by the priority date of the subject application. For example, ERT was approved for treatment of "Gaucher's disease[,] . . . the oldest and most common lysosomal storage disease," in 1991. Specification at [004], [0101]. Although commercial development of ERT for other lysosomal storage disorders came later, animal studies had already indicated the broad utility of ERT approaches for the treatment of lysosomal storage disorders years before Applicants' invention.[7] *See, e.g.*, Kikuchi et al., *J. Clin. Invest.* 101:827-833 (1998) (ERT in quail model of Pompe disease); Scaravilli and Suzuki, *Nature* 305:713-715 (1983)[8] (ERT in murine model of Krabbe disease); Kakkis et al., *Biochem. Mol. Med.* 58:156-167 (1996)[9] (ERT in canine model of MPS I); Bielicki et al., *J. Biol. Chem.* 274:36335-36343 (1999) (ERT in feline model of MPS VI); Byers et al., *Bone* 21:425-431 (1997) (ERT in feline model of MPS VI); Vogler et al., *Pediatr. Res.* 45:838-844 (1999) (ERT in murine model of MPS VII); O'Connor et al., *J. Clin. Invest.* 101:1394-1400 (1998) (ERT in murine model of MPS VII). *See also* specification at [018]-[020].

Thus, the skilled artisan would have expected enzyme replacement therapy to be effective for a wide range of lysosomal storage diseases. Indeed, that expectation has been borne out by the considerable number of ERT therapies that have since been approved and commercially marketed, including, e.g., Fabrazyme® (Genzyme Corp.; Fabry disease), Myozyme® (Genzyme Corp.; Pompe disease), Aldurazyme® (Genzyme Corp. and BioMarin Pharmaceutical, Inc.; MPS I), Elaprase™ (Shire; MPS II), Replagal™ (Shire; Fabry disease), and Naglazyme® (BioMarin Pharmaceutical, Inc., MPS VI).

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[7] Commercial availability of a therapy is not an appropriate test for lack of enablement because it is dependent on factors that are independent of technical feasibility, such as, e.g., the size of the affected population, the cost of pre-clinical and clinical trials, and the availability of funding.

[8] This document was submitted in an IDS initialed by the Examiner on May 21, 2007.

[9] This document was submitted in an IDS initialed by the Examiner on May 21, 2007.

(1) Prospect of Partial Responses

The Examiner alleges that the claimed invention is not enabled because of the "prospect that only *partial responses* may occur, despite prolonged treatment."[10] Office Action at 9 (emphasis added). The Examiner also argues that "Eto et al. . . . points out that '[m]ost lysosomal storage diseases have central nervous system (CNS) involvement. No effective treatment is available at present." *Id.* at 9. Applicants respectfully traverse.

Applicants first note that "Office personnel should not impose a 35 U.S.C. 112, first paragraph, rejection grounded on a 'lack of utility' basis unless a 35 U.S.C. 101 rejection is proper." M.P.E.P. § 2107.01. In the present case, a rejection under 35 U.S.C. § 101 would clearly be improper, as the M.P.E.P. specifically teaches that "it is improper for Office personnel to request evidence . . . regarding the degree of effectiveness." M.P.E.P. § 2107.03 (emphasis in original). Further, "Office personnel should not . . . require that an applicant demonstrate that a therapeutic agent based on a claimed invention is a . . . fully effective drug for humans." M.P.E.P. § 2107.01. Indeed, "[a]n assertion that the claimed invention is useful in treating a symptom of an incurable disease may be considered credible . . . on the basis of a fairly modest amount of evidence or support. *Id.*

Applicants further note that *Pastores*, cited by the Examiner, teaches that treatment of non-CNS aspects of a LSD may be helpful to patients exhibiting neurological symptoms. For example, although "[n]eurological improvement is . . . limited in treated patients with type III [Gaucher disease] . . . the reversal of the extraneurological disease has been associated with improved quality of life." *Pastores* at 894. *Pastores* also teaches that ERT for mucopolysaccharidosis I, "[a]lthough not likely to have a significant direct effect on CNS pathology, . . . will lead to indirect

[10] The Examiner cites Wraith, *J. Inherit. Metab. Dis.* 29:442-447 (2006) ("*Wraith*") for that proposition. However, *Wraith* also teaches that "[i]n my experience, patients suffering from a progressive LSD would be happy if the treatment made the underlying condition stable and prevented further deterioration." *Wraith* at 444.

positive effects on cognitive function." *Id.* at 895. Accordingly, any prospect of partial responses is not evidence of lack of enablement.

(2) Membrane Proteins

The Examiner argues that "Pastores points out that several disorders [are] associated with defects in membrane proteins and these diseases will most likely not [be] responsive to enzyme therapy or substrate reduction." Office Action at 8.

Even if ERT were ineffective for a limited number of disorders, the mere presence of inoperative embodiments is not grounds for an enablement rejection. M.P.E.P. § 2164.08(b). *See also In re Wands*, 858 F.2d 731 (Fed. Cir. 1988) (concluding that screening many hybridomas to find the few that fell within the claims was not undue experimentation). Indeed, the M.P.E.P. teaches that "[t]he standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." M.P.E.P. § 2164.08(b). In the instant case, the skilled artisan could readily determine which lysosomal enzymes are membrane proteins, and potentially inoperative, with minimal effort.

Further, Applicants note that although *Pastores* speaks of "[s]everal" membrane proteins (naming two), *Pastores* describes "[t]he majority of LSDs that represent therapeutic targets [as] primarily those resulting from a deficiency of an enzyme or soluble hydrolase." *Pastores* at 897. *See also Salvetti* at 107 ("Many enzymes implicated in LSD are secreted proteins with the notable exception of glucocerebrosidase [which is a commercially available ERT] and acid phosphatase that behave like membrane-associated proteins").

For all of the reasons above, it is clear that the full breadth of the claims with regard to enzyme replacement therapy is adequately enabled, and that the skilled artisan could make and use the claimed invention without undue experimentation. Therefore, Applicants respectfully request that the enablement rejection with regard to enzyme replacement therapy be withdrawn.

D. Administration Routes

The Examiner alleges that "[t]he specification fails to provide adequate guidance and evidence for how to treat a subject . . . via various administration routes so as to provide therapeutic effect and to ameliorate the symptoms of the disease." Office Action at 5-6. Applicants respectfully disagree.

The M.P.E.P. explains that if "the art recognizes that standard modes of administration are known and contemplated, 35 U.S.C. 112 is satisfied." M.P.E.P. § 2164.01(c). Indeed, both the USPTO and the courts have consistently held that "a patent need not teach, and preferably omits, what is well known in the art. " *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384 (Fed. Cir. 1986) (citation omitted). Specifically, a "patent disclosure need not enable information within the knowledge of an ordinarily skilled artisan. *Thus, a patentee preferably omits from the disclosure any routine technology that is well known at the time of application.*" *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254 (Fed. Cir. 2004) (citations omitted) (emphasis added). *See also* M.P.E.P. § 2163.

The specification teaches that "methods for administering the combination therapies of the invention include all methods . . . well known in the art." Specification at [089]. Neither gene therapy nor enzyme replacement therapy is the subject of the invention, and suitable administration routes for each were well known to the skilled artisan. Moreover, the specification discloses exemplary administration routes at [008]-[017], [018]-[020], [0100], [0106], and Examples 1, 3-6 and 8-12. Accordingly, it is clear that the full breadth of the claims with regard to administration routes is adequately enabled, and that the skilled artisan could make and use the claimed invention without undue experimentation. Therefore, Applicants respectfully request that that the enablement rejection with regard to administration routes be withdrawn.

IV. Conclusion

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: December 3, 2007

By: _____
Nicole L. M. Valtz
Reg. No. 47,150